**KETOCONAZOLE - ketoconazole tablet**
Mylan Pharmaceuticals Inc.

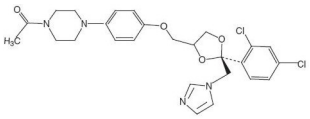
**Rx only**

**WARNING**

**When used orally, ketoconazole has been associated with hepatic toxicity, including some fatalities. Patients receiving this drug should be informed by the physician of the risk and should be closely monitored. (See WARNINGS and PRECAUTIONS sections.)**
**Coadministration of terfenadine with ketoconazole tablets is contraindicated. Rare cases of serious cardiovascular adverse events, including death, ventricular tachycardia and torsades de pointes have been observed in patients taking ketoconazole tablets concomitantly with terfenadine, due to increased terfenadine concentrations induced by ketoconazole tablets. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS sections.)**
**Pharmacokinetic data indicate that oral ketoconazole inhibits the metabolism of astemizole, resulting in elevated plasma levels of astemizole and its active metabolite desmethylastemizole which may prolong QT intervals. Coadministration of astemizole with ketoconazole tablets is therefore contraindicated. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS sections.)**
**Coadministration of cisapride with ketoconazole is contraindicated. Serious cardiovascular adverse events including ventricular tachycardia, ventricular fibrillation and torsades de pointes have occurred in patients taking ketoconazole concomitantly with cisapride. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS sections.)**

## DESCRIPTION

Ketoconazole is a synthetic broad-spectrum antifungal agent available in scored white tablets, each containing 200 mg ketoconazole base for oral administration. In addition, each tablet also contains the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone and starch (corn). Ketoconazole is *cis*-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxyl]phenyl]piperazine.
Ketoconazole is a white to slightly beige, odorless powder, soluble in acids, with a molecular weight of 531.44. Ketoconazole's structural formula and molecular formula are as follows:



$C_{26}H_{28}Cl_2N_4O_4$

## CLINICAL PHARMACOLOGY

Mean peak plasma levels of approximately 3.5 mcg/mL are reached within 1 to 2 hours, following oral administration of a single 200 mg dose taken with a meal. Subsequent plasma elimination is biphasic with a half-life of 2 hours during the first 10 hours and 8 hours thereafter. Following absorption from the gastrointestinal tract, ketoconazole is converted into several inactive metabolites. The major identified metabolic pathways are oxidation and degradation of the imidazole and piperazine rings, oxidative O-dealkylation and aromatic hydroxylation. About 13% of the dose is excreted in the urine, of which 2 to 4% is unchanged drug. The major route of excretion is through the bile into the intestinal tract. *In vitro*, the plasma protein binding is about 99% mainly to the albumin fraction. Only a negligible proportion of ketoconazole reaches the cerebral-spinal fluid. Ketoconazole is a weak dibasic agent and thus requires acidity for dissolution and absorption.
Ketoconazole tablets are active against clinical infections with *Blastomyces dermatitidis*, *Candida spp.*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, and *Phialophora spp.* Ketoconazole tablets are also active against *Trichophyton spp.*, *Epidermophyton spp.*, and *Microsporum spp*. Ketoconazole is also active *in vitro* against a variety of fungi and yeast. In animal models, activity has been demonstrated against *Candida spp.*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Malassezia furfur*, *Coccidioides immitis*, and *Cryptococcus neoformans.*

### Mode of Action

*In vitro* studies suggest that ketoconazole impairs the synthesis of ergosterol, which is a vital component of fungal cell membranes.

## INDICATIONS AND USAGE

Ketoconazole tablets are indicated for the treatment of the following systemic fungal infections: candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. Ketoconazole tablets should not be used for fungal meningitis because it penetrates poorly into the cerebral-spinal fluid.
Ketoconazole tablets are also indicated for the treatment of patients with severe recalcitrant cutaneous dermatophyte infections who have not responded to topical therapy or oral griseofulvin, or who are unable to take griseofulvin.

## CONTRAINDICATIONS

Coadministration of terfenadine or astemizole with ketoconazole tablets is contraindicated. (See BOX WARNING, WARNINGS, and PRECAUTIONS sections.)

Concomitant administration of ketoconazole tablets with cisapride is contraindicated. (See BOX WARNING, WARNINGS and PRECAUTIONS sections.)

Concomitant administration of ketoconazole tablets with oral triazolam is contraindicated. (See PRECAUTIONS section.)

Ketoconazole is contraindicated in patients who have shown hypersensitivity to the drug.

## WARNINGS

**Hepatotoxicity, primarily of the hepatocellular type, has been associated with the use of ketoconazole tablets, including rare fatalities. The reported incidence of hepatotoxicity has been about 1:10,000 exposed patients, but this probably represents some degree of under-reporting, as is the case for most reported adverse reactions to drugs. The median duration of ketoconazole tablet therapy in patients who developed symptomatic hepatotoxicity was about 28 days, although the range extended to as low as 3 days. The hepatic injury has usually, but not always, been reversible upon discontinuation of ketoconazole tablet treatment. Several cases of hepatitis have been reported in children.**

Prompt recognition of liver injury is essential. Liver function tests (such as SGGT, alkaline phosphatase, SGPT, SGOT and bilirubin) should be measured before starting treatment and at frequent intervals during treatment. Patients receiving ketoconazole tablets concurrently with other potentially hepatotoxic drugs should be carefully monitored, particularly those patients requiring prolonged therapy or those who have had a history of liver disease.

Most of the reported cases of hepatic toxicity have to date been in patients treated for onychomycosis. Of 180 patients worldwide developing idiosyncratic liver dysfunction during ketoconazole tablet therapy, 61.3% had onychomycosis and 16.8% had chronic recalcitrant dermatophytoses.

Transient minor elevations in liver enzymes have occurred during treatment with ketoconazole tablets. The drug should be discontinued if these persist, if the abnormalities worsen, or if the abnormalities become accompanied by symptoms of possible liver injury.

**In rare cases anaphylaxis has been reported after the first dose.** Several cases of hypersensitivity reactions including urticaria have also been reported.

Coadministration of ketoconazole tablets and terfenadine has led to elevated plasma concentrations of terfenadine which may prolong QT intervals, sometimes resulting in life-threatening cardiac dysrhythmias. Cases of torsades de pointes and other serious ventricular dysrhythmias, in rare cases leading to fatality, have been reported among patients taking terfenadine concurrently with ketoconazole tablets. Coadministration of ketoconazole tablets and terfenadine is contraindicated.

Coadministration of astemizole with ketoconazole tablets is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and PRECAUTIONS sections.)

Concomitant administration of ketoconazole tablets with cisapride is contraindicated because it has resulted in markedly elevated cisapride plasma concentrations and prolonged QT interval, and has rarely been associated with ventricular arrhythmias and torsades de pointes. (See BOX WARNING, CONTRAINDICATIONS and PRECAUTIONS sections.)

In European clinical trials involving 350 patients with metastatic prostatic cancer, eleven deaths were reported within two weeks of starting treatment with high doses of ketoconazole tablets (1200 mg/day). It is not possible to ascertain from the information available whether death was related to ketoconazole therapy in these patients with serious underlying disease. However, high doses of ketoconazole tablets are known to suppress adrenal corticosteroid secretion.

In female rats treated three to six months with ketoconazole at dose levels of 80 mg/kg and higher, increased fragility of long bones, in some cases leading to fracture, was seen. The maximum "no-effect" dose level in these studies was 20 mg/kg (2.5 times the maximum recommended human dose). The mechanism responsible for this phenomenon is obscure. Limited studies in dogs failed to demonstrate such an effect on the metacarpals and ribs.

## PRECAUTIONS

### General

Ketoconazole tablets have been demonstrated to lower serum testosterone. Once therapy with ketoconazole has been discontinued, serum testosterone levels return to baseline values. Testosterone levels are impaired with doses of 800 mg per day and abolished by 1600 mg per day. Ketoconazole tablets also decrease ACTH induced corticosteroid serum levels at similar high doses. The recommended dose of 200 mg to 400 mg daily should be followed closely.

In four subjects with drug-induced achlorhydria, a marked reduction in ketoconazole absorption was observed. Ketoconazole tablets require acidity for dissolution. If concomitant antacids, anticholinergics, and $H_2$-blockers are needed, they should be given at least two hours after administration of ketoconazole tablets. In cases of achlorhydria, the patients should be instructed to dissolve each tablet in 4 mL aqueous solution of 0.2 N HCl. For ingesting the resulting mixture, they should use a drinking straw so as to avoid contact with the teeth. This administration should be followed with a cup of tap water.

**Information for Patients**

**Patients should be instructed to report any signs and symptoms which may suggest liver dysfunction so that appropriate biochemical testing can be done. Such signs and symptoms may include unusual fatigue, anorexia, nausea and/or vomiting, jaundice, dark urine or pale stools (see WARNINGS section).**

**Drug Interactions**

Ketoconazole is a potent inhibitor of the cytochrome P450 3A4 enzyme system. Coadministration of ketoconazole tablets and drugs primarily metabolized by the cytochrome P450 3A4 enzyme system may result in increased plasma concentrations of the drugs that could increase or prolong both therapeutic and adverse effects. Therefore, unless otherwise specified, appropriate dosage adjustments may be necessary. The following drug interactions have been identified involving ketoconazole tablets and other drugs metabolized by the cytochrome P450 enzyme system.

Ketoconazole tablets inhibit the metabolism of terfenadine, resulting in an increased plasma concentration of terfenadine and a delay in the elimination of its acid metabolite. The increased plasma concentration of terfenadine or its metabolite may result in prolonged QT intervals. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS sections.)

Pharmacokinetic data indicate that oral ketoconazole inhibits the metabolism of astemizole, resulting in elevated plasma levels of astemizole and its active metabolite desmethylastemizole which may prolong QT intervals. Coadministration of astemizole with ketoconazole tablets is therefore contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS sections.)

Human pharmacokinetics data indicate that oral ketoconazole potently inhibits the metabolism of cisapride resulting in a mean eight-fold increase in AUC of cisapride. Data suggest that coadministration of oral ketoconazole and cisapride can result in prolongation of the QT interval on the ECG. Therefore concomitant administration of ketoconazole tablets with cisapride is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS sections.)

Ketoconazole tablets may alter the metabolism of cyclosporine, tacrolimus, and methylprednisolone, resulting in elevated plasma concentrations of the latter drugs. Dosage adjustment may be required if cyclosporine, tacrolimus, or methylprednisolone are given concomitantly with ketoconazole tablets.

Coadministration of ketoconazole tablets with midazolam or triazolam has resulted in elevated plasma concentrations of the latter two drugs. This may potentiate and prolong hypnotic and sedative effects, especially with repeated dosing or chronic administration of these agents. These agents should not be used in patients treated with ketoconazole tablets. If midazolam is administered parenterally, special precaution is required since the sedative effect may be prolonged.

Rare cases of elevated plasma concentrations of digoxin have been reported. It is not clear whether this was due to the combination of therapy. It is, therefore, advisable to monitor digoxin concentration in patients receiving ketoconazole.

When taken orally, imidazole compounds like ketoconazole may enhance the anticoagulant effect of coumarin-like drugs. In simultaneous treatment with imidazole drugs and coumarin drugs, the anticoagulant effect should be carefully titrated and monitored.

Because severe hypoglycemia has been reported in patients concomitantly receiving oral miconazole (an imidazole) and oral hypoglycemic agents, such a potential interaction involving the latter agents when used concomitantly with ketoconazole tablets (an imidazole) can not be ruled out.

Concomitant administration of ketoconazole tablets with phenytoin may alter the metabolism of one or both of the drugs. It is suggested to monitor both ketoconazole and phenytoin.

Concomitant administration of rifampin with ketoconazole tablets reduces the blood levels of the latter. INH (Isoniazid) is also reported to affect ketoconazole concentrations adversely. These drugs should not be given concomitantly.

After the coadministration of 200 mg oral ketoconazole twice daily and one 20 mg dose of loratadine to 11 subjects, the AUC and $C_{max}$ of loratadine averaged 302% (± 142 S.D.) and 251% (± 68 S.D.), respectively, of those obtained after co-treatment with placebo. The AUC and $C_{max}$ of descarboethoxyloratadine, an active metabolite, averaged 155% (± 27 S.D.) and 141% (± 35 S.D.), respectively. However, no related changes were noted in the $QT_c$ on ECG taken at 2, 6, and 24 hours after the coadministration. Also, there were no clinically significant differences in adverse events when loratadine was administered with or without ketoconazole.

Rare cases of a disulfiram-like reaction to alcohol have been reported. These experiences have been characterized by flushing, rash, peripheral edema, nausea, and headache. Symptoms resolved within a few hours.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

The dominant lethal mutation test in male and female mice revealed that single oral doses of ketoconazole as high as 80 mg/kg produced no mutation in any stage of germ cell development. The *Ames Salmonella* microsomal activator assay was also negative. A long term feeding study in Swiss Albino mice and in Wistar rats showed no evidence of oncogenic activity.

**Pregnancy**

Teratogenic Effects. Pregnancy Category C

Ketoconazole has been shown to be teratogenic (syndactylia and oligodactylia) in the rat when given in the diet at 80 mg/kg/day (10 times the maximum recommended human dose). However, these effects may be related to maternal toxicity, evidence of which also was seen at this and higher dose levels.

There are no adequate and well controlled studies in pregnant women. Ketoconazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects
Ketoconazole has also been found to be embryotoxic in the rat when given in the diet at doses higher than 80 mg/kg during the first trimester of gestation.

In addition, dystocia (difficult labor) was noted in rats administered oral ketoconazole during the third trimester of gestation. This occurred when ketoconazole was administered at doses higher than 10 mg/kg (higher than 1.25 times the maximum human dose).

It is likely that both the malformations and the embryotoxicity resulting from the administration of oral ketoconazole during gestation are a reflection of the particular sensitivity of the female rat to this drug. For example, the oral $LD_{50}$ of ketoconazole given by gavage to the female rat is 166 mg/kg whereas in the male rat the oral $LD_{50}$ is 287 mg/kg.

**Nursing Mothers**
Since ketoconazole is probably excreted in the milk, mothers who are under treatment should not breast feed.

**Pediatric Use**
Ketoconazole tablets have not been systematically studied in children of any age, and essentially no information is available on children under 2 years. Ketoconazole should not be used in pediatric patients unless the potential benefit outweighs the risks.

## ADVERSE REACTIONS
**In rare cases, anaphylaxis has been reported after the first dose.** Several cases of hypersensitivity reactions including urticaria have also been reported. However, the most frequent adverse reactions were nausea and/or vomiting in approximately 3%, abdominal pain in 1.2%, pruritus in 1.5%, and the following in less than 1% of the patients: headache, dizziness, somnolence, fever and chills, photophobia, diarrhea, gynecomastia, impotence, thrombocytopenia, leukopenia, hemolytic anemia, and bulging fontanelles. Oligospermia has been reported in investigational studies with the drug at dosages above those currently approved. Oligospermia has not been reported at dosages up to 400 mg daily, however sperm counts have been obtained infrequently in patients treated with these dosages. Most of these reactions were mild and transient and rarely required discontinuation of ketoconazole tablets. In contrast, the rare occurrences of hepatic dysfunction require special attention (see WARNINGS section).
In worldwide postmarketing experience with ketoconazole tablets there have been rare reports of alopecia, paresthesia, and signs of increased intracranial pressure including bulging fontanelles and papilledema. Hypertriglyceridemia has also been reported but a causal association with ketoconazole is uncertain.
Neuropsychiatric disturbances, including suicidal tendencies and severe depression, have occurred rarely in patients using ketoconazole tablets.
Ventricular dysrhythmias (prolonged QT intervals) have occurred with the concomitant use of terfenadine with ketoconazole tablets. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS sections.) Data suggest that coadministration of ketoconazole tablets and cisapride can result in prolongation of the QT interval and has rarely been associated with ventricular arrhythmias. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS sections.)

## OVERDOSAGE
In the event of accidental overdosage, supportive measures, including gastric lavage with sodium bicarbonate, should be employed.

## DOSAGE AND ADMINISTRATION

**Adults**
The recommended starting dose of ketoconazole tablets is a single daily administration of 200 mg (one tablet). In very serious infections or if clinical responsiveness is insufficient within the expected time, the dose of ketoconazole may be increased to 400 mg (two tablets) once daily.

**Children**
In small numbers of children over 2 years of age, a single daily dose of 3.3 to 6.6 mg/kg has been used. Ketoconazole tablets have not been studied in children under 2 years of age.
There should be laboratory as well as clinical documentation of infection prior to starting ketoconazole therapy. Treatment should be continued until tests indicate that active fungal infection has subsided. Inadequate periods of treatment may yield poor response and lead to early recurrence of clinical symptoms. Minimum treatment for candidiasis is one or two weeks. Patients with chronic mucocutaneous candidiasis usually require maintenance therapy. Minimum treatment for the other indicated systemic mycoses is six months.
Minimum treatment for recalcitrant dermatophyte infections is four weeks in cases involving glabrous skin. Palmar and plantar infections may respond more slowly. Apparent cures may subsequently recur after discontinuation of therapy in some cases.

**HOW SUPPLIED**

Ketoconazole Tablets, USP are available containing 200 mg of ketoconazole. The 200 mg tablets are white to off-white, round, flat-faced, beveled edge tablets debossed with **M** above the score and **261** below the score on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-0261-01
bottles of 100 tablets
NDC 0378-0261-05
bottles of 500 tablets

**STORE AT ROOM TEMPERATURE**
**15° TO 30°C (59° TO 86°F).**
**PROTECT FROM MOISTURE.**

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
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